

# Baroreflex-Mediated Heart Rate and Vascular Resistance Responses 24 h after Maximal Exercise

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## ABSTRACT

CONVERTINO, V. A. Baroreflex-Mediated Heart Rate and Vascular Resistance Responses 24 h after Maximal Exercise. *Med. Sci. Sports Exerc.*, Vol. 35, No. 6, pp. 970–977, 2003. **Introduction.** Plasma volume, heart rate (HR) variability, and stimulus-response relationships for baroreflex control of forearm vascular resistance (FVR) and HR were studied in eight healthy men after and without performing a bout of maximal exercise to test the hypotheses that acute expansion of plasma volume is associated with 1) reduction in baroreflex-mediated HR response, and 2) altered operational range for central venous pressure (CVP). **Methods.** The relationship between stimulus ( $\Delta$ CVP) and vasoconstrictive reflex response ( $\Delta$ FVR) during unloading of cardiopulmonary baroreceptors was assessed with lower-body negative pressure (LBNP, 0, -5, -10, -15, -20 mm Hg). The relationship between stimulus ( $\Delta$ mean arterial pressure (MAP)) and cardiac reflex response ( $\Delta$ HR) during loading of arterial baroreceptors was assessed with steady-state infusion of phenylephrine (PE) designed to increase MAP by 15 mm Hg alone and during application of LBNP (PE+LBNP) and neck pressure (PE+LBNP+NP). Measurements of vascular volume and autonomic baroreflex responses were conducted on two different test days, each separated by at least 1 wk. On one day, baroreflex response was tested 24 h after graded cycle exercise to volitional exhaustion. On another day, measurement of baroreflex response was repeated with no exercise (control). The order of exercise and control treatments was counterbalanced. **Results.** Baseline CVP was elevated ( $P = 0.04$ ) from a control value of  $10.5 \pm 0.4$  to  $12.3 \pm 0.4$  mm Hg 24 h after exercise. Average  $\Delta$ FVR/ $\Delta$ CVP during LBNP was not different ( $P = 0.942$ ) between the exercise ( $-1.35 \pm 0.32$  pru-mm Hg $^{-1}$ ) and control ( $-1.32 \pm 0.36$  pru-mm Hg $^{-1}$ ) conditions. However, maximal exercise caused a shift along the reflex response relationship to a higher CVP and lower FVR. HR baroreflex response ( $\Delta$ HR/ $\Delta$ MAP) to PE+LBNP+NP was lower ( $P = 0.015$ ) after maximal exercise ( $-0.43 \pm 0.15$  beats $\cdot$ min $^{-1}$  $\cdot$ mm Hg $^{-1}$ ) compared with the control condition ( $-0.83 \pm 0.14$  beats $\cdot$ min $^{-1}$  $\cdot$ mm Hg $^{-1}$ ). **Conclusion.** Expansion of vascular volume after acute exercise is associated with altered operational range for CVP and reduced HR response to arterial baroreceptor stimulation. **Key Words:** AUTONOMIC FUNCTION, BLOOD PRESSURE, CENTRAL VENOUS PRESSURE, PHENYLEPHRINE, NECK PRESSURE, LOWER BODY NEGATIVE PRESSURE, COUNTERMEASURES

Increased incidence of orthostatic hypotension and intolerance in humans is associated with vascular hypovolemia and attenuated cardiovascular reflex functions (3,11,15,16,18–22,31,33,37). Specifically, attenuation of the carotid-cardiac baroreflex has accompanied orthostatic compromise reported in healthy human subjects (9,11,21–23,33) and occurred independent of reductions in blood volume (11,44). On the other hand, reduced circulating blood volume appears to be a primary underlying cause for the accentuated tachycardia and peripheral vasoconstriction that accompanies given arterial and cardiopulmonary baroreceptor stimulation (10,44). It is therefore not surpris-

ing that blood volume and carotid-cardiac baroreflex sensitivity have been reported to be independent predictors of orthostatic tolerance (19,33). Thus, any treatment that would prove effective in increasing cardiac and vasoconstrictive baroreflex responses or reserves, and/or blood volume could prove effective as a therapeutic countermeasure against development of orthostatic hypotension and intolerance.

Performance of a single bout of graded exercise designed to elicit maximal effort has ameliorated hemodynamic compromise and/or orthostatic hypotension and intolerance in human subjects exposed to extended spaceflight, bed rest, or wheelchair confinement (11,21,22,36,43). This effect may not be surprising because the short-term impacts of maximal exercise included expansion (25) or restoration (13) of blood volume, and increased sensitivity of the carotid-cardiac baroreflex (8,21,22,29,42). However, we are unaware of any data that describe the effect of acute maximal exercise on the reflex HR response to arterial baroreceptor stimulation and vascular response to cardiopulmonary baroreceptor stimulation. Because reserves for eliciting tachycardia and peripheral vasoconstriction are reduced by hypovolemia (10,44), we hypothesized that expanded blood volume associated with acute maximal exercise would cause

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a reduced reflex response (i.e., greater reserve) of HR and peripheral vascular resistance to arterial and cardiopulmonary baroreceptor stimulation, respectively. The purpose of this investigation was to test this hypothesis.

## METHODS

**Subjects.** After being informed of all procedures and risks, eight healthy, normotensive, nonsmoking men with mean ( $\pm$  SE) age of  $27 \pm 2$  yr (range 20–35), height of  $177 \pm 4$  cm (range 160–180), and weight of  $81.5 \pm 4.1$  kg (range 61.4–90.9) gave their written consent to serve as subjects for this investigation. All experimental procedures and protocols were approved by the Human Research Review Boards at Brooks Air Force Base and the U.S. Army Institute of Surgical Research. Selection of subjects was based on results of a screening evaluation comprised of a detailed medical history, physical examination, blood chemistry analysis, urinalysis, and electrocardiogram (ECG). Subjects were made familiar with all laboratory personnel, procedures, and protocols during an orientation session conducted before the study.

**General protocol.** On a random basis, each subject completed two experimental treatments that entailed tests of autonomic function (a) after performance of a maximal exercise bout, and (b) during a control (no exercise) session. A minimum of 1 wk intervened between the two experimental test sessions. Subjects maintained their normal sleep pattern, refrained from exercise, and abstained from caffeine and other autonomic stimulants such as prescription and nonprescription drugs for at least 48 h before each experimental protocol. To minimize possible circadian effects, both experimental protocols were initiated at the same time of day.

On one occasion, subjects performed a multistage cycle ergometer exercise protocol in the upright posture to voluntary exhaustion with autonomic function tests conducted at 24 h postexercise. The subjects were instructed to control their physical activity to sitting and minimal walking for both the exercise and control treatments during the 24 h before data collection periods. With the exception of the maximal exercise bout, the same protocol was followed on the control experimental day.

Subjects underwent the following measurements once 24 h after the exercise condition and once under the control (no exercise) condition: (a) baseline vagal tone by analysis of baseline R-R interval variability; (b) forearm blood flow response to graded, nonhypotensive lower-body negative pressure (LBNP); (c) heart rate (HR) response to graded elevations in mean arterial pressure (MAP); and (d) plasma volume. During all tests, continuous HR was measured from an ECG. These tests were conducted over a period of approximately 2 h on each test day.

**R-R interval variability.** An ECG was continuously recorded during 5 min in which subjects were instructed to breathe at a respiratory rate matched to a metronome that was set at a frequency of 0.25 Hz (15 breaths per minute). The ECG was digitized at a sampling rate of 1000 Hz and

analyzed with a microcomputer. R-R intervals were measured at an accuracy of 1 ms using R-wave detection software. Time series comprising 256 consecutive R-R intervals were selected and an index of baseline cardiac vagal activity was assessed by calculating the standard deviation of R-R intervals (30).

**Measurement of baroreceptor control of blood flow.** Subjects were required to lie in a LBNP device in the right lateral decubitus position with the right arm dependent for measurements of peripheral venous pressure (PVP). Before initializing the LBNP protocol, a 20-gauge Teflon<sup>®</sup> catheter (Angioset) was inserted into an antecubital vein of the dependent right arm that was used to continuously monitor PVP during the LBNP test. With the right arm being suspended, the valves in the veins become incompetent, resulting in an unimpeded column of blood. Under these conditions, the pressure in the large vein of the right arm reflect central venous pressure (estimated CVP) when the pressure transducer is centered at heart level (24). The catheter was then cleared with isotonic saline solution and connected to a Baxter Uniflow<sup>™</sup> model 43-260 pressure transducer (Baxter Healthcare Corp., Irvine, CA) for measurement of venous pressure. Before connection to the catheter, the transducer was positioned at the level of the mid-sternum with a ruler and level, and was calibrated with a known 20 mm Hg pressure introduced from an Omega<sup>®</sup> digital manometer (Omega Engineering Inc., Stamford, CT). Care was taken to use a specially designed ruler and level to ensure accurate, repeatable location of the transducer for subsequent estimated CVP determinations.

The left arm was raised to heart level and used for forearm blood flow (FBF) measurements. FBF was measured by venous occlusion plethysmography, using a Whitney mercury-in-silastic strain gauge placed around the left forearm with circulation to the hand occluded. Baseline systolic and diastolic arterial blood pressures were measured noninvasively from the left arm with a sphygmomanometer before the silastic strain gauge was placed on the forearm. After instrumentation for FBF measurements, the LBNP protocol was initiated. The LBNP protocol began with a 2-min baseline rest period with the LBNP pressure at 0 mm Hg followed by continuous decompression of 5 mm Hg every 2 min down to  $-20$  mm Hg. At the end of 2 min at  $-20$  mm Hg LBNP, the sphygmomanometer was replaced on the left arm, and systolic and diastolic arterial blood pressure measurements were repeated. MAP was calculated by dividing the sum of systolic pressure and twice diastolic pressure by three. In agreement with previously reported data (12), there was no statistical difference ( $P = 0.656$ ) between MAP at baseline ( $82.8 \pm 2.4$  mm Hg) and at  $-20$  mm Hg ( $82.4 \pm 2.6$  mm Hg). Therefore, an index of forearm vascular resistance (FVR) at baseline and each level of LBNP was calculated by dividing the average of MAP at baseline and  $-20$  mm Hg by forearm blood flow and expressed as peripheral resistance units (PRU,  $\text{mm Hg} \cdot \text{min}^{-1} \cdot 100 \text{ mL}^{-1} \cdot \text{mL}^{-1}$ ). The LBNP protocol was designed to selectively elicit the vascular constriction response caused by unloading the cardiopulmonary baroreceptors.

HR and estimated CVP were measured continuously throughout the LBNP test, and forearm blood flow was recorded every 20 s. Estimated CVP at rest and each level of LBNP was determined by averaging the continuous measure of estimated CVP recorded during the last 1.5 min of each 2-min level, while FBF was the average of the six measurements during each level. Linear regression analysis was used to calculate the slope of the stimulus-response relationship (i.e., baroreflex gain) between estimated CVP and forearm vascular resistance (6). Data collected from our laboratory have demonstrated excellent reproducibility in the measurement of this baroreflex response as indicated by intraclass correlation coefficient ( $r$ ) for test-retest reliability of 0.86 ( $N = 14$ ) and day-to-day variation over 10 wk of 0.36 mm Hg (3.2%) (6).

**Measurement of arterial baroreceptor-cardiac reflex responses.** After measurement of the cardiopulmonary baroreflex response, baroreflex control of HR was assessed using a technique previously described (10,17). The subject remained in the LBNP chamber at a right lateral decubitus position and with the 20-gauge catheter inserted into the antecubital vein of the dependent right arm for measurement of estimated CVP. In addition, a second 20-gauge catheter was inserted into an antecubital vein of the left arm for drug infusion. Beat-by-beat arterial blood pressures were measured noninvasively by the Finapres<sup>®</sup> finger-cuff blood pressure monitoring device (Ohmeda Inc., Englewood, CO). After instrumentation, subjects rested quietly for 15 min, after which 3 min of resting baseline HR and blood pressure data were obtained. The protocol was initiated with a steady-state infusion (Baxter pump) of phenylephrine (PE) into the left arm catheter with a goal of increasing MAP by 15 mm Hg. LBNP was applied (ranging from 5 to 20 mm Hg) until estimated CVP was returned to pre-PE infusion levels (PE+LBNP), and neck pressure equal to 1.4 times the increase in MAP (32) was then applied to the anterior two-thirds of the neck (PE+LBNP+NP). Responsiveness of arterial baroreflex control of HR was calculated as the ratio of the difference in HR to MAP ( $\Delta\text{HR}/\Delta\text{MAP}$ ) between pre-PE infusion and post-PE infusion with LBNP and neck pressure.

**Plasma measurements.** Plasma volume was determined by a modified dilution technique (13,27) using sterile solutions of Evans blue dye contained in 10-mL ampules (The New World Trading Corp., DeBary, FL). After each subject was stabilized in the supine position for at least 90 min after the completion of LBNP, a preinjection control blood sample was drawn followed by an intravenous injection of 11.5 mg of dye diluted with isotonic saline solution (2.5 mL) that was administered through a sterile 0.45 micron filter. One milliliter of plasma from a 10-min postinjection blood sample was passed through a wood-cellulose powder (Solka-Floc SW-40A) chromatographic column so that the dye could be absorbed. The absorbed dye was eluted from the column using a 1:1 water-acetone solution (pH = 7.0) and collected in a 10-mL volumetric flask. The postinjection solution was compared with 1-mL samples from a preinjection time (zero control) and a standard dye solution (1:50

dilution with distilled water), and all samples were read at 615 nm with a spectrophotometer. Using these procedures in our laboratory, test-retest correlation coefficient for blood volume was 0.85–0.97 with average changes of 82 mL (average  $\%\Delta = 1.5\%$ ,  $N = 17$ ), 75 mL (average  $\%\Delta = 1.5\%$ ,  $N = 19$ ), 56 mL (average  $\%\Delta = 1.1\%$ ,  $N = 23$ ), and 25 mL (average  $\%\Delta = 0.7\%$ ,  $N = 7$ ) when measurements were determined 4 d, 8 d, 15 d, and 11 months apart, respectively (13,27). During baseline rest, 10 mL of blood was taken without stasis from the left arm catheter to determine the response of norepinephrine (NE) and epinephrine (E). Immediately after each withdrawal, whole blood was taken from the syringe, transferred to a chilled tube containing sodium EDTA, and centrifuged at 2000 g for 20 min at 4°C. Immediately after centrifugation, the plasma was aliquoted for NE and E, and stored frozen until analyses were performed. Plasma NE and E concentrations were measured by high-performance liquid chromatography (Waters Corp., Milford, MA) according to standardized procedures (3,5,13). Total circulating NE and E were calculated as the product of plasma volume and plasma concentrations of NE and E, respectively.

**Statistics.** Standard descriptive statistics were performed on each of the response variables of interest with results presented as means  $\pm$  SE. Standard paired  $t$ -test statistics were used to compare mean slopes of the stimulus-response relationship between CVP and FVR (i.e.,  $\Delta\text{FVR}/\Delta\text{CVP}$ ) during cardiopulmonary baroreflex testing, mean ratios of the stimulus-response relationship between MAP and HR (i.e.,  $\Delta\text{HR}/\Delta\text{MAP}$ ) during arterial baroreflex testing, mean values for baseline circulating catecholamines and plasma volume, and mean values for standard deviation of R-R intervals. Exact  $t$ - and  $P$ -values are presented for each independent effect and reflect the probability of obtaining the observed effect given only randomization error (1).

## RESULTS

**Exercise bout.** Final work rate at volitional fatigue averaged  $1600 \pm 60$  kpm $\cdot\text{min}^{-1}$  and was attained after a mean time of  $17.6 \pm 0.6$  min. HR and systolic and diastolic blood pressures at termination averaged  $186 \pm 3$  bpm,  $183 \pm 2$  mm Hg, and  $77 \pm 3$  mm Hg, respectively.

**Baseline hemodynamic status.** Average body weight 24 h after maximal exercise ( $83.4 \pm 4.4$  kg) was similar ( $t = 1.061$ ,  $P = 0.324$ ) to that for the control condition ( $83.1 \pm 4.4$  kg). Baseline HR and arterial blood pressures were statistically unaltered ( $t \leq 0.880$ ,  $P \geq 0.408$ ) by maximal exercise compared with the control condition (Table 1).

**Indices of baseline autonomic activity.** The average standard deviation of R-R intervals during controlled breathing was not statistically distinguishable ( $t = 1.299$ ,  $P = 0.235$ ) between the exercise ( $62.2 \pm 12.2$  ms) and control ( $55.0 \pm 8.7$  ms) conditions. Likewise, there was no statistical difference in total circulating plasma NE



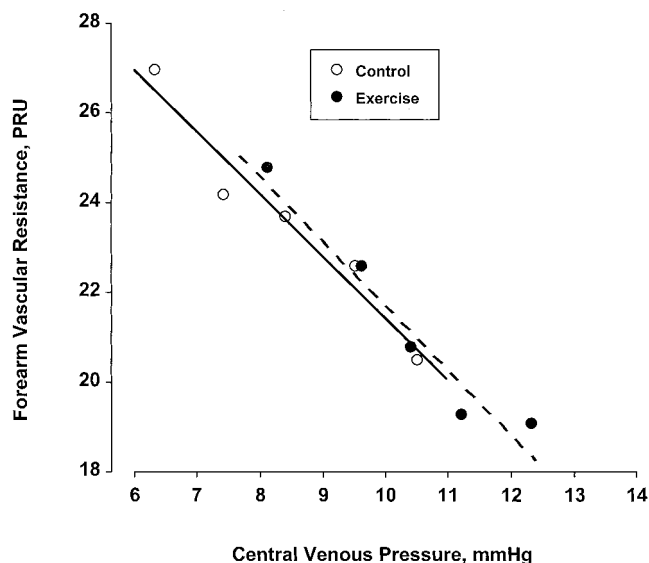
TABLE 1. Subject baseline descriptive data.

	Control	Exercise	<i>t</i>	<i>P</i>
Body weight (kg)	83.1 ± 4.4	83.4 ± 4.3	1.061	0.324
Systolic BP (mm Hg)	113 ± 2	115 ± 4	0.449	0.667
Diastolic BP (mm Hg)	68 ± 3	66 ± 3	0.880	0.408
Mean BP (mm Hg)	83 ± 2	82 ± 2	0.369	0.723
Heart rate (bpm)	59 ± 1	59 ± 3	0.068	0.947
R-R variability (ms)	55.0 ± 8.7	62.2 ± 12.2	1.299	0.235
Plasma NE (pg)	500 ± 72	480 ± 63	0.279	0.788
Plasma Epi (pg)	39.3 ± 13.3	49.6 ± 19.2	0.491	0.638

and E between exercise and control treatments at baseline rest (Table 1).

**Relationship between baseline CVP and plasma volume.** Estimated baseline CVP was increased ( $t = 3.076$ ;  $P = 0.018$ ) from a control value of  $10.5 \pm 0.4$  to  $12.3 \pm 0.4$  mm Hg 24 h after exercise. When compared with the control treatment ( $3711 \pm 133$  mL), acute maximal exercise resulted in an average 10% expansion ( $t = 6.497$ ,  $P = 0.0003$ ) of plasma volume ( $4081 \pm 153$  mL).

**Baroreflex control of peripheral vascular resistance.** Average stimulus-response relationships of the baroreflex control of FVR for exercise and control treatments are plotted in Figure 1. Differences in slopes ( $\Delta\text{FVR}/\Delta\text{CVP}$ ) between the exercise and control conditions were compared by analyzing the least squares linear estimates generated by each subject. The average slope of the reflex response (i.e.,  $\Delta\text{FVR}/\Delta\text{CVP}$ ) was not different ( $t = 0.076$ ;  $P = 0.942$ ) between the exercise ( $-1.35 \pm 0.32$  pru·mm Hg $^{-1}$ ) and control ( $-1.32 \pm 0.36$  pru·mm Hg $^{-1}$ ) conditions, but the reflex response relationship was shifted along the reflex response relationship to a higher CVP and lower FVR (Fig. 1).



**FIGURE 1**—Baroreflex stimulus-response relationship between estimated central venous pressure (CVP) and forearm vascular resistance (FVR) at control (open circles and solid line) and 24 h after maximal exercise (closed circles and broken line). Circles represent the mean of all subjects ( $N = 8$ ) at baseline,  $-5$ ,  $-10$ ,  $-15$ , and  $-20$  mm Hg LBNP under each experimental condition. The linear equation for the mean control response is  $\text{FVR} = -1.39 (\text{CVP}) + 35.3$  ( $r^2 = 0.948$ ) and for the mean exercise response is  $\text{FVR} = -1.46 (\text{CVP}) + 36.4$  ( $r^2 = 0.945$ ).

TABLE 2. Heart rate and mean arterial pressure responses to three experimental protocols with and without (control) maximal exercise.

	Baseline	PE	PE + LBNP	PE + LBNP + NP
HR (bpm)				
Control	61 ± 1	49 ± 3*	49 ± 3*	50 ± 2*
Maximal exercise	59 ± 3	51 ± 3*	50 ± 3*	51 ± 3*
MAP (mm Hg)				
Control	89.4 ± 2.0	104.5 ± 2.8*	103.2 ± 3.9*	103.6 ± 3.6*
Maximal exercise	84.3 ± 3.1	99.3 ± 2.5*	100.4 ± 3.2*	103.2 ± 3.1*

Values are means ± SE.

PE, steady-state phenylephrine infusion; LBNP, lower-body negative pressure; NP, neck pressure.

\*  $P < 0.05$  vs baseline.

**Arterial baroreflex control of HR.** Responses of HR and MAP during stages of PE, PE+LBNP, and PE+LBNP+NP are presented in Table 2. By design, infusion of PE caused a similar ( $t = 0.147$ ,  $P = 0.888$ ) elevation ( $t = 19.02$ ,  $P < 0.0001$ ) in average MAP of  $15.2 \pm 1.2$  mm Hg in the control condition compared with  $14.9 \pm 1.2$  mm Hg in the exercise condition. Average elevations ( $P < 0.0001$ ) in estimated CVP of  $5.6 \pm 1.0$  mm Hg (control) and  $4.9 \pm 0.9$  mm Hg (maximal exercise) induced by PE infusion were returned to baseline levels by application of similar ( $t = 0.569$ ,  $P = 0.479$ ) LBNP levels of  $-17.5 \pm 0.2$  mm Hg during control and  $-17.7 \pm 0.2$  mm Hg during exercise conditions. Similarly, the level of neck pressure was indistinguishable ( $t = 0.1745$ ,  $P = 0.691$ ) between control ( $21.1 \pm 1.7$  mm Hg) and exercise ( $20.1 \pm 1.7$  mm Hg) conditions.

Calculated arterial baroreceptor-cardiac reflex response ( $\Delta\text{HR}/\Delta\text{MAP}$ ) to PE+LBNP+NP was reduced in all eight subjects such that the average gain of the cardiac baroreflex response was lower ( $t = 3.376$ ,  $P = 0.015$ ) 24 h after maximal exercise ( $0.43 \pm 0.15$  beats·min $^{-1}$ ·mm Hg $^{-1}$ ) compared with control ( $0.83 \pm 0.14$  beats·min $^{-1}$ ·mm Hg $^{-1}$ ). Conversely, the difference in  $\Delta\text{HR}/\Delta\text{MAP}$  between the PE+LBNP+NP condition and PE+LBNP alone condition was greater ( $t = 2.643$ ,  $P = 0.038$ ) 24 h after maximal exercise ( $0.23 \pm 0.11$  beats·min $^{-1}$ ·mm Hg $^{-1}$ ) compared with control ( $0.05 \pm 0.12$  beats·min $^{-1}$ ·mm Hg $^{-1}$ ).

## DISCUSSION

**Elevated CVP after maximal exercise as a mechanism for rather than a consequence of plasma volume expansion?** Maximal exercise has been used as a model to induce expansion of plasma volume by as much as 10–16% within 24 h (13,25,26). We used this technique to increase plasma volume by an average of 10% in the subjects of the present investigation and measured the stimulus-response relationship between estimated CVP and peripheral (forearm) vascular resistance to test the notion that the hypervolemia induced by maximal exercise might be associated with a “resetting” of the operational range for CVP to a higher level. Although the absolute operational range for CVP was not altered by exercise ( $\Delta\text{CVP} = 4.2$  mm Hg), the results of this study demonstrated that the range around which CVP operated during cardiopulmonary baroreceptor stimulation was higher after maximal exercise

(12.3–8.1 mm Hg) than during the control condition (10.5–6.3 mm Hg).

Exercise-induced hypervolemia with elevated CVP has been reported in both cross-sectional and longitudinal comparisons (14,41). Mechanisms associated with plasma volume expansion that occurs within the completion of a single bout of maximal exercise include secretion of hormones related to control of fluid-electrolyte homeostasis, increased thirst, increased plasma protein synthesis, and renal retention of sodium and water (26,28,37–40,45). Despite activation of these mechanisms, expansion of plasma volume would be difficult in the absence of an increase in the operating point for the sensing of volume by receptors on the low-pressure side of the cardiovascular system. We previously hypothesized that the elevation of CVP that accompanies exercise-induced hypervolemia might represent a “resetting” of the operational point for regulation of vascular volume rather than a simple physical result of increased volume (14). The shift of the stimulus-response relationship between CVP and peripheral vascular resistance to a higher operating level for CVP (Fig. 1) is consistent with the notion that maximal exercise increases the operational point for regulation of vascular volume.

**HR responses to arterial baroreceptor stimulation.** We measured HR during phenylephrine infusion under conditions of controlled LBNP and LBNP with neck pressure for comparison of cardiac responses to similar stimulation in subjects from other investigations with varying blood volumes (10,17,41). Attenuated HR response to stimulation by PE+LBNP+NP was associated with expanded blood volume in physically fit subjects (41), whereas contraction of plasma volume during physical inactivity (bed rest) was associated with accentuated HR responses (17). When plasma volume was acutely contracted independent of exercise, the cardiac response to stimulation by PE+LBNP+NP was increased compared with a normovolemic response (10). Taken together, the results from these experiments suggested that vascular volume contributes to the responsiveness (gain) of arterial-cardiac baroreflex responses. We therefore hypothesized that our subjects in the present investigation would demonstrate decreased HR response during phenylephrine infusion with LBNP and neck pressure because of their expanded plasma volume. Our results support our hypothesis.

Although our experiment was not designed to identify mechanism(s) for altered HR responses to alterations in arterial pressure after acute maximal exercise, several possibilities may be discussed based on our results. The absence of change in baseline HR, blood pressures, circulating catecholamines, and R-R interval variability suggest that there was probably no significant alteration in either baseline sympathetic or parasympathetic neural activity within 24 h after maximal exercise. Also, there appeared to be no alteration in cardiac adrenergic receptor responsiveness in these subjects (7). Taken together, these data suggest that reduced HR reflex responses to arterial baroreceptor stimulation could not be explained by changes in autonomic reflex function. Therefore, it appears most likely that the attenu-

ated arterial-cardiac baroreflex response observed in our subjects after acute maximal exercise represents an appropriate blunted response associated with greater circulating vascular volume.

Using an acute model of maximal exercise in the absence of physical training, we induced a 10% expansion of plasma volume and a 17% increase in estimated baseline central venous pressure when compared with the nonexercise control condition. The hypervolemic state was of a magnitude characteristic of that observed in a trained compared with a sedentary state (2,14,34,35,41). In the present investigation, increases in plasma volume and CVP were associated with a 48% decrease in HR response to PE+LBNP+NP. Our data are proportionately comparable to the observation that 19% greater plasma volume and 37% higher CVP in highly aerobic fit individuals compared with average fit individuals was associated with a 76% attenuation in HR response to PE+LBNP+NP (41). Because higher plasma volumes, increased CVP, and reduced HR response to PE+LBNP+NP were associated with greater maximal oxygen uptakes, the investigators suggested that high aerobic fitness may contribute to autonomic adaptations that underlie attenuated baroreflex function (41). However, the results of the present investigation are unique in that they demonstrated acute hypervolemia in the absence of prolonged physical training was associated with an attenuated HR response to PE+LBNP+NP. Our data provide an alternative explanation that reduced HR baroreflex responses reported in individuals who exercise may result from an appropriate response associated with proportionate increases in exercise-induced hypervolemia rather than impaired baroreflex function.

Using a single-bolus phenylephrine-infusion technique, Somers et al. (42) demonstrated an increased HR baroreflex response per unit change in MAP in hypertensive patients 60 min after the completion of maximal exercise. Subsequent investigations provided evidence that the isolated carotid-cardiac baroreflex response was increased within 24 h after maximal exercise (8,22,29). Because the carotid-cardiac baroreflex response has been represented by the difference in HR response during phenylephrine infusion between LBNP alone and LBNP+NP (6,10,17,41), we hypothesized that the difference in HR response between PE+LBNP and PE+LBNP+NP in our subjects would be increased with maximal exercise. Our results are consistent with this hypothesis and provide evidence that the increased HR baroreflex response observed by Somers and coworkers was possibly due to carotid baroreflex changes in a time course that occurred before expansion of vascular volume could have an impact on total arterial-cardiac reflex responsiveness.

Using rapid beat-to-beat fluctuations in carotid pressure stimuli and measured R-R intervals to characterize the pressure input-vagal nerve output relationship of the carotid-cardiac baroreflex (18), carotid-cardiac baroreflex responsiveness has been shown repeatedly to increase within 24 h after maximal exercise (8,22,29). In previous experiments, we have also demonstrated that the HR response to changes in arterial blood pressure during a Valsalva maneuver was

increased 24 h after maximal exercise (20,21). Measurements of arterial-cardiac baroreflex responses conducted in the present investigation extended previous observations by providing specific stimuli to arterial baroreceptors 24 h after maximal exercise and provide new insight into the interpretations of previous results. First, the increased HR response to alterations in arterial blood pressure during the Valsalva maneuver after maximal exercise in previous studies most likely represents carotid baroreceptor control because HR responses to total arterial baroreceptor stimuli were attenuated 24 h after exercise in the present investigation. Second, our data may be the first to demonstrate a link between increased vagal nerve response to carotid baroreceptor stimuli induced by a single bout of maximal exercise (8,22,29) and increased HR response to carotid baroreceptor stimuli (present study).

**Peripheral vascular resistance responses to cardiopulmonary baroreceptor stimulation.** In previous experiments, we reported increased vasoconstrictive reserve and reduced orthostatic hypotension when maximal exercise was performed after 16 d of head-down bed rest (22) and by patients with spinal cord injury (20). Larger blood volumes have been associated with less vasoconstriction (i.e., peripheral vascular resistance) under equal orthostatic challenge (34,35,44). Based on measurements of forearm vascular resistance, our results in this study uniquely demonstrate that the cardiovascular system remains vasodilated in response to increased CVP and plasma volume. With evidence that compensatory vasoconstriction during orthostasis has a maximal capacity (4,22), increased peripheral vasodilation at equal LBNP levels after the maximal exercise condition in the present investigation suggests that exhaustive leg ergometry increased the capacity to vasoconstrict by shifting the CVP-FVR stimulus-response relationship to a higher CVP and lower FVR. Therefore, the results of our study may be the first to demonstrate that increased CVP and plasma volume are associated with a vasodilated cardiovascular system and provide a mechanism for the increased maximal vasoconstrictive reserve 24 h after maximal exercise reported in previously investigations (20,22).

The reduction in circulating blood volume induced by confinement to bed rest is associated with an accentuated vasoconstrictive response to reductions in CVP (12), whereas a blunted vasoconstrictive response to baroreceptor stimulation is associated with exercise training-induced hypervolemia (34). Similar responses in vascular resistance to graded reductions in CVP can be produced by acute reductions and expansions of blood volume (44), suggesting that vascular volume is a primary factor that dictates the responsiveness (gain) of the cardiopulmonary baroreflex response. In this regard, we hypothesized that the maximum slope of the CVP-FVR stimulus-response relationship that we measured in our subjects would be reduced 24 h after maximal exercise with the acute expansion of circulating vascular volume. Against expectations, responsiveness (slope) of the CVP-FVR stimulus-response relationship was not altered in our subjects (Fig. 1). A possible explanation for the absence of an attenuated baroreflex response in FVR after acute

expansion of vascular volume in the present study is that the sensitivity of reflex vasoaction was increased by maximal exercise. This possibility is consistent with previous findings (20–22). Nevertheless, it is clear that the preservation of vasoconstrictive responsiveness in the presence of hypervolemia reflects that the acute phase of adaptation to maximal exercise uniquely alters the relationship between circulating blood volume and baroreflex responsiveness.

**Limitations.** Interpretation of cardiac reflex responses to arterial baroreceptor stimulation by the PE infusion technique used in this study is made with an understanding of certain limitations in experimental manipulations. Clamping of CVP and carotid pressure at resting baseline levels during PE infusion by application of LBNP and neck pressure, respectively, has been used to remove PE-induced loading of cardiopulmonary and carotid baroreceptors, thereby isolating the influence of the aortic baroreceptors (6,10,17,41). However, the ability to “clamp” or “isolate” baroreceptor stimulation during the use of PE in combination with LBNP and NP in human subjects cannot be substantiated with our experimental methods. More importantly, when NP was superimposed on the PE infusion and LBNP stimuli under steady-state conditions in the present study, there were insignificant alterations in HR (Table 2). This observation may reflect rapid adaptation of reflex HR responses in the presence of concurrent vascular reflex adjustments and raise doubt to meaningful interpretations regarding the specific functions of aortic and carotid baroreceptor reflexes (6,10,17,41). Therefore, we chose to focus our discussions and interpretations on reflex HR responses to total arterial baroreceptor stimulation in comparison with results in the literature rather than on carotid and aortic baroreflex paradigms.

Because only a single point elevation in blood pressure was elicited, the complete sigmoidal characteristic of the arterial-cardiac baroreflex relationship could not be described. Rather than cause an actual reduction in the HR response to total arterial baroreceptor stimulation, it is possible that acute maximal exercise altered the relationship between the position of the operational point (baseline HR and blood pressure) and baroreflex curve such that we measured the HR response on a flatter portion of the same stimulus-response curve. However, results from previous investigations that defined arterial-cardiac baroreflex responses after acute or chronic exercise indicated that elevations of 35 mm Hg in arterial pressure remained in the linear portion of the stimulus-response relationship (41). Further, baseline HR and arterial blood pressures were unaltered by maximal exercise. Although we cannot completely dismiss the possibility that the alterations in arterial-cardiac baroreflex response observed in our subjects after maximal exercise would be influenced by movement of the baseline HR and blood pressure to a flatter, nonlinear portion of the sigmoidal baroreflex stimulus-response relationship (i.e., saturation), it seems unlikely.

By design, PE alone increased MAP by approximately 15 mm Hg in both control and exercise conditions. Addition of LBNP and LBNP+NP to PE infusion returned CVP to



baseline levels but did not alter MAP compared with the PE alone. Without a change in arterial pressure, there was no stimulus to induce a reflex change in HR. These results are identical to our previous experiences with this technique (17). Our data indicate that stimuli to baroreceptors (i.e., pressure changes) were reproducible and well controlled. Therefore, it is unlikely that our interpretation that changes in HR reflex responses were induced by maximal exercise should be affected by potential limitations of the method for arterial baroreflex measurement.

We acknowledge that blood volume by itself is not the only explanation for our observations about the relationship between expanded blood volume and baroreflex responses. It is possible that the exercise-induced blood volume expansion observed in the present investigation increased stroke volume and cardiac output, which in turn resulted in the observed shift on the stimulus-response relationship (particularly for FVR responses). Therefore, in the absence of stroke volume and cardiac output measurements, we make our interpretations with the caveat that acute maximal exercise might affect HR and vascular resistance responses in alterations to arterial and venous blood pressures through mechanisms other than simple changes in vascular volume.

**Conclusions.** The primary finding of the present investigation was that expanded blood volume associated with acute maximal exercise caused a reduced reflex response of HR and peripheral (forearm) vascular resistance (i.e., greater vasoconstrictive reserve) to aortic and cardiopulmonary baroreceptor stimulation, respectively. The relationship between reduced HR response to arterial baroreceptor stimulation in the presence of expanded blood volume in this study provides one possible explanation for tachycardia that

is observed in hypovolemic states such as those induced by dehydration, spaceflight and bed rest. Because hypovolemia reduces orthostatic tolerance, acute expansion of blood volume has clinical implications for protection or recovery of normal physiological function in bedridden patients and astronauts. The implication for failure of CVP and plasma volume to return to baseline levels for as long as 24 h after maximal exercise in the present investigation is that the operational range for feedback regulation of vascular volume was increased. Our results may be the first to demonstrate that increased CVP and plasma volume induced by maximal exercise is associated with a vasodilated cardiovascular system. Therefore, the shift of the stimulus-response relationship for the control of peripheral vascular resistance to an elevated operating range of central venous pressure may represent a fundamental mechanism by which maximal exercise has proven to be an effective acute therapeutic countermeasure against the clinical consequences of central hypovolemia and orthostatic hypotension.

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